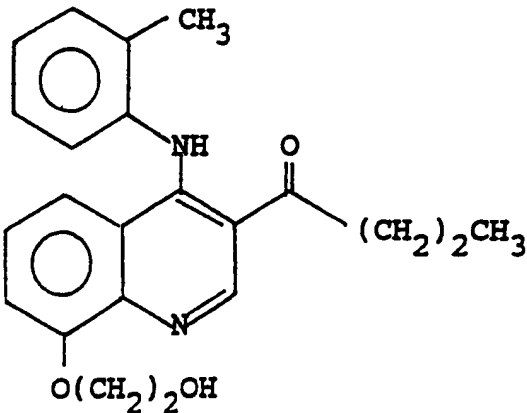


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07D 215/44, A61K 31/47</p>	<p>A1</p>	<p>(11) International Publication Number: WO 92/12969 (43) International Publication Date: 6 August 1992 (06.08.92)</p>
<p>(21) International Application Number: PCT/EP92/00200 (22) International Filing Date: 27 January 1992 (27.01.92) (30) Priority data: 9101918.2 29 January 1991 (29.01.91) GB 9101919.0 29 January 1991 (29.01.91) GB (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM INTERCREDIT B.V. [NL/NL]; Jaagpad 1, P.O. Box 3120, NL-2280 GC Rijswijk (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): IFE, Robert, John [GB/GB]; LEACH, Colin, Andrew [GB/GB]; Smithkline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).</p>		<p>(74) Agent: GIDDINGS, Peter, J.; Corporate Patents, Smith-Kline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US. Published With international search report.</p>
<p>(54) Title: SALTS OF A 4-AMINO-3-ACYL QUINOLINE DERIVATIVE AND THEIR USE AS INHIBITORS OF GASTRIC ACID SECRETION</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>A compound of structure (I) in the form of a salt, a process for its preparation and pharmaceutical compositions comprising such a salt and its use in therapy.</p>		

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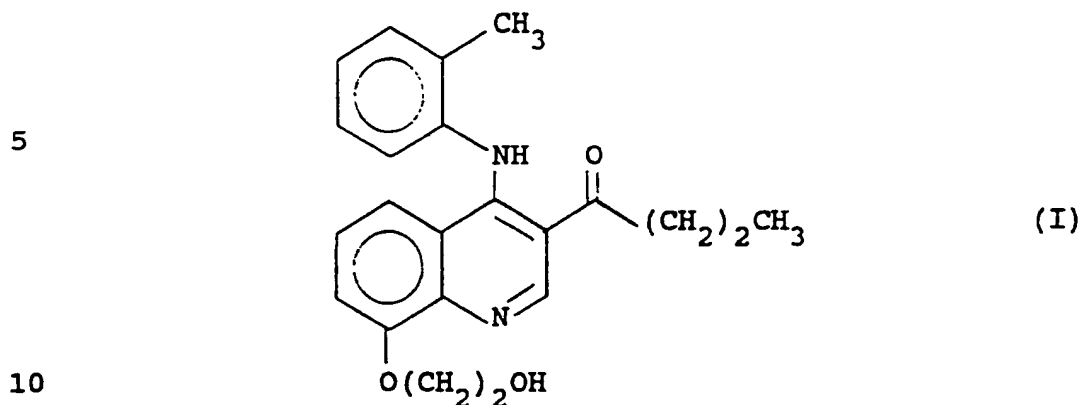
Salts of a 4-amino-3-acyl quinoline derivative and their use as inhibitors of gastric acid secretion.

The present invention relates to certain salts of a quinoline compound, pharmaceutical compositions
5 containing them and their use in therapy as inhibitors of gastric acid secretion.

Quinoline compounds which have activity as gastric acid secretion inhibitors are known in the art, for
10 example, EP-330485-A discloses a series of 4-amino-3-acylquinoline derivatives in which the quinoline is substituted in the 8-position by, for example, hydroxyalkyl and hydroxyalkoxy groups.

15 The compounds of EP 330485-A have been found to have poor dissolution rates in water and, as a consequence, could potentially exhibit poor bioavailability in vivo and hence low and poorly reproducible levels of therapeutic activity. It has now been found that the
20 problem of poor dissolution can be overcome by producing the compounds in the form of a particular class of salts. Furthermore, in selecting compounds for use in therapy it is important to take a number of criteria into account, for example, in addition to physical qualities
25 such as good dissolution (and hence good bioavailability), the desired level of intrinsic potency and duration of action of the chosen compounds has to be at the desired level. It has been found that a particular compound of EP-330485-A when produced in the
30 form of a salt as described herein, in addition to having the desired physical qualities such as a high dissolution rate, also has the desired levels of potency and duration of action and, as such, forms the subject matter of the present invention.

The present invention therefore provides in a first aspect a compound of structure (I):



in the form of a salt characterised in that the salt is that formed by reaction of said compound of structure (I) with a strong acid.

15

As used herein, the term strong acid shall be taken to mean an acid with a pka of less than about 4.0. The nature of such acids will be apparent to those skilled in the art and include, for example, mineral acids such as hydrochloric acid, and sulphonic acids such as alkyl sulphonic acids, in particular methane sulphonic acid.

20

Particularly preferred salts of the present invention are those formed by reaction with hydrochloric acid or methane sulphonic acid, that is to say, 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline hydrochloride, and 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline mesylate.

25

30

The salts of the present invention, in particular the hydrochloride and mesylate salts referred to above, have been found to exhibit exceptionally fast intrinsic dissolution rates when compared to the free base compound of structure (I) disclosed in EP-330485-A. Thus,

whereas the free base has a poor dissolution rate and, as such, may be expected in vivo to exhibit poorly reproducible bioavailability (and so be less effective therapeutically), the salts of the present invention are
5 expected to exhibit a much more consistent bioavailability (since their dissolution rates are far more favourable) and to prove more effective per given dose and more reliably effective per given dose on administration to patients.

10

The salts described herein can be used in therapy in the treatment of gastrointestinal diseases in mammals, in particular humans. Such diseases include, for example, gastric and duodenal ulcers, aspiration pneumonitis and
15 Zollinger-Ellison syndrome. Further, the salts can be used in the treatment of other disorders where an anti-secretory effect is desirable, for example in patients with a history of chronic and excessive alcohol consumption, and in patients with gastrooesophageal
20 reflux disease (GERD).

In therapeutic use, the salts can be administered in a standard pharmaceutical composition comprising the salt and a pharmaceutically acceptable carrier. The present
25 invention provides in a further aspect therefore a pharmaceutical composition comprising a salt as described herein in association with a pharmaceutically acceptable carrier.

30 Suitable pharmaceutical compositions are as described in EP-330485-A.

Suitable daily dosage regimens for an adult patient may be, for example, an oral dose of between 1 and
35 1000 mg, preferably between 1 and 500 mg, or an

intravenous, subcutaneous or intramuscular dose of between 0.1 and 100 mg, preferably between 0.1 and 25 mg of the salts described herein, the salt being administered in a unit dosage 1 to 4 times a day.

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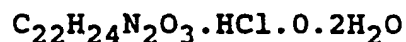
In addition, the salts can be co-administered with further active ingredients such as antacids (for example, magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-inflammatory drugs, steroids or nitrite
10 scavengers or other drugs used for treating gastric ulcers (for example, prostanoids or H₂-antagonists such as cimetidine).

EXAMPLE 1

3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-
quinoline can be prepared according to the procedures
5 described in EP-330485-A.

Preparation of 3-butyryl-4-(2-methylphenylamino)-8-(2-
hydroxyethoxy)quinoline hydrochloride

10 3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxy-
ethoxy)quinoline (10 g) was suspended in methanol (100 ml)
at room temperature, conc. hydrochloric acid added slowly
to give a clear solution, then the solvent evaporated.
The residue was twice taken up in 2-propanol and
15 re-evaporated, and was then recrystallised from
2-propanol/ether to obtain the desired salt (9.7 g),
m.p. 214-215°C.



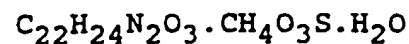
Found C 65.50, H 6.21, N 6.88

20 Requires C 65.32, H 6.33, N 6.93.

EXAMPLE 2

25 Preparation of 3-butyryl-4-(2-methylphenylamino)-8-(2-
hydroxyethoxy)quinoline mesylate

3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxy-
ethoxy)quinoline (60 g) was suspended in ethyl acetate
(400 ml), warmed to 50°C, and methanesulphonic acid
30 (16.3 g) added with vigorous stirring. The desired salt
crystallised on cooling, and was filtered off and washed
with ethyl acetate; yield 50.1 g, m.p. 83-85°C.

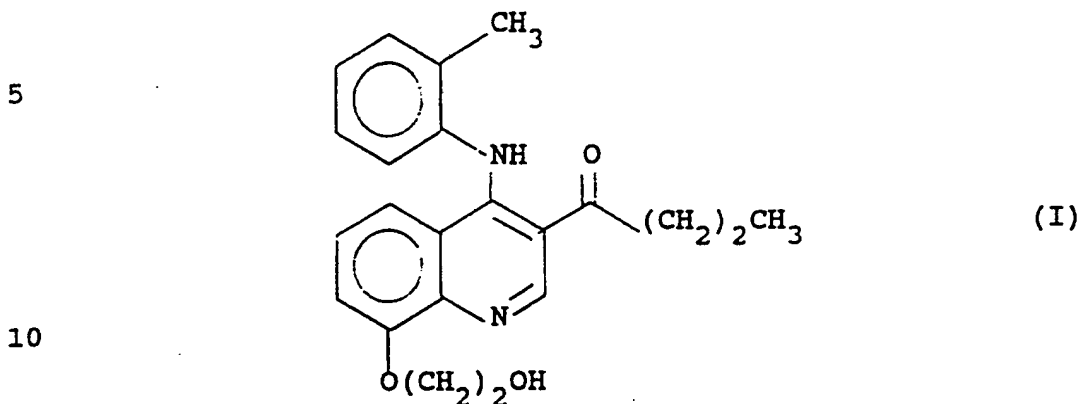


Found C 57.78, H 6.28, N 5.84

35 Requires C 57.73, H 6.32, N 5.85.

Claims

1. A compound of structure (I):



15 in the form of a salt, characterised in that the salt is that formed by reaction of the compound of structure (I) with a strong acid.

- 20 2. A salt according to claim 1 which is 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline hydrochloride.

3. A salt according to claim 1 which is 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline mesylate.

- 25 4. A process for preparing a salt according to claim 1 which comprises reacting a compound of structure (I) as described in claim 1 with a strong acid.

- 30 5. A pharmaceutical composition comprising a salt according to claim 1 in association with a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising
3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-
quinoline hydrochloride in association with a
pharmaceutically acceptable carrier.

5

7. A salt according to claim 1 for use in therapy.

8. 3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxy-
ethoxy)quinoline hydrochloride for use in therapy.

10

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07D215/44; A61K31/47		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP,A,0 330 485 (SMITHKLINE BECKMAN INTERCREDIT B.V.) 30 August 1989 cited in the application see page 3, line 19 - line 23 see page 6, line 31 - line 34; claims 1,6-9; example 10 <div style="text-align: center;">---</div>	1-8
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>⁹ Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
1	Date of the Actual Completion of the International Search <div style="text-align: center; font-weight: bold;">03 APRIL 1992</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold;">12.05.92</div>
International Searching Authority <div style="text-align: center; font-weight: bold;">EUROPEAN PATENT OFFICE</div>		Signature of Authorized Officer <div style="text-align: center;"> P. BOSMA </div>

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

**EP 9200200
SA 55460**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0330485	30-08-89	AU-B- 606508	07-02-91
		AU-A- 3181989	22-09-89
		WO-A- 8908104	08-09-89
		JP-T- 2503318	11-10-90
